HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

The new Clinical Trial Regulation (CTR) explained-

General principles – Session 1, November 22, 2021

Elaine Breslin MB BCH BAO, PhD, FRCPI, Clinical Assessment Manager

22-25 November, 2021

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Clinical Trials Directive (CTD) vs Clinical Trials Regulation (CTR)

Clinical Trials Directive (CTD) 2001/20/EC

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Aims:

- provide greater protection to CT participants
- ensure quality of conduct
- strengthen responsibilities of sponsors and Member States (MSs)
- harmonise regulation and conduct of clinical trials throughout Europe

Clinical Trials Directive=
achievements but also **shortcomings**

CTD – Shortcomings

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Fragmentation of the authorisation process

- Independent assessment by National Competent Authorities (NCA)
- Independent assessment by ethics committees

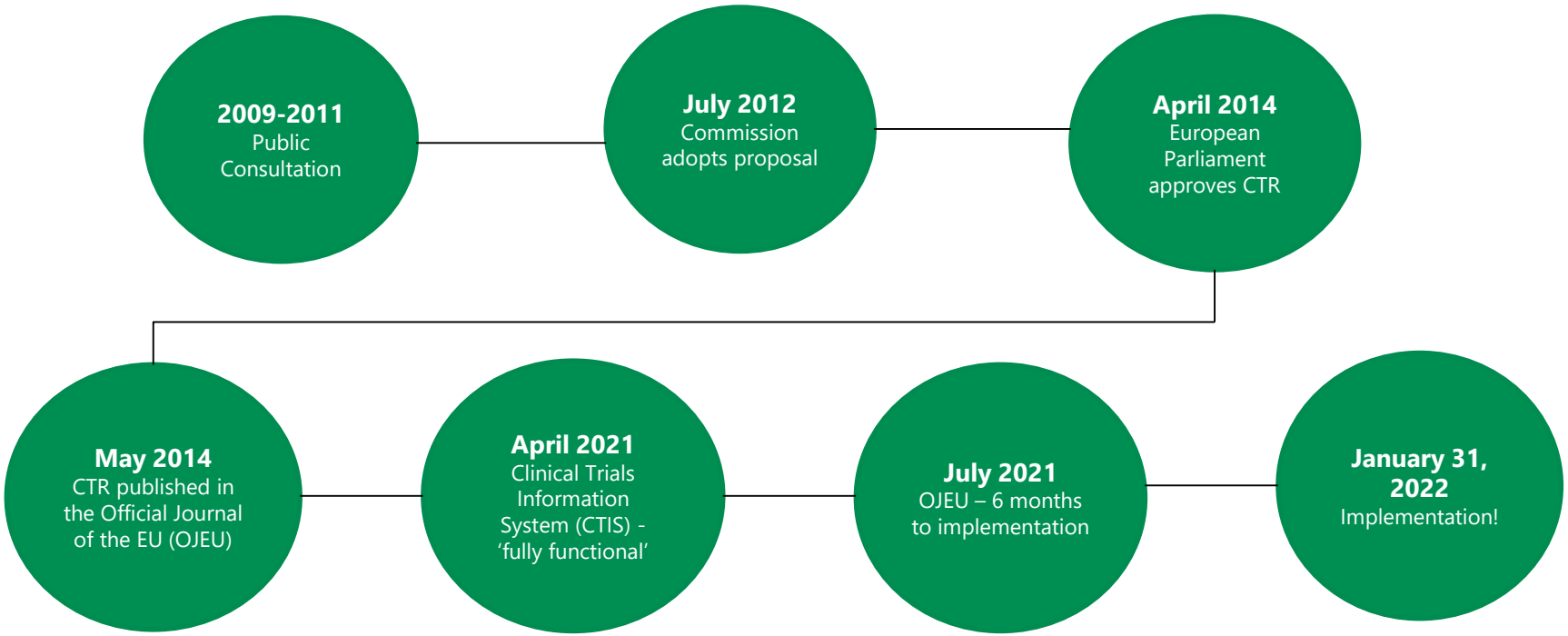
Lack of harmonisation

- National laws
- Different interpretation of the directive/guidelines
- Different approach to assessment

Divergent decisions
= delays & cost-implications

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Improving clinical trials legislation: key dates



Implementation of CTR

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

- Implementation of Directive via national law

- **Direct** implantation of Regulation –identical rules throughout the EU (*national law deals only with national aspects)

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

CTR – general principles

CTR – benefits include

- **Harmonisation** of application & authorisation – benefit for conduct of multi-national trials
- Sponsor **options** re application process
- **Clarification** of rules on protection of subjects
- **Transparency**

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

CTR - Application & Authorisation

Harmonisation – application & authorisation

- **Single** entry point – Clinical Trials Information System (CTIS)
- **Single** set of documents submitted by sponsor to multiple MSs
- **Single** IMPD/IB for trials with same sponsor and same concerned Member States (MSCs), can cross-refer to authorised IMPD/IB
- **Single** fee per MS
- **Single** authorisation procedure for all CTs (mono & multi-national) within strict timelines
- **Single** reporting MS (RMS) leads coordinated assessment
- **Single** national decision and authorisation per MS
- **Single** substantial modification, if applicable, to many CTs

CTR - Tacit validation and approval

- Validation
- Approvals are
  - Active i.e. notification by RMS/MSC
  - Tacit if no notification and timeline expires
- **No minimal timelines for approval**

CTR - Additional options for the sponsor

- New application:
  - **complete** application (Part I and II aspects) submitted to all MSCs
  - **staggered** application – Part I and II submitted to some MSCs, and Part I only to other MSCs
  - **two-phase** assessment - submission Part I and if positive conclusion, submission of Part II up to 2 years later
- Following authorisation, can **add a MSC**
- CT can start in MSC following positive decision in that MSC (don't need to wait for all MSC's decisions)

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

CTR - Protection of vulnerable subjects

CTR - Informed consent procedures clarified

Clinical trials in incapacitated subjects

Pregnant or breastfeeding women

Clinical trials in minors

Clinical trials in emergency situations

Informed consent in cluster trials

CTR - Vulnerable groups - enrolment criteria

Emergency trials	•Direct benefit ONLY
Clinical trials on minors	•Direct benefit •Some benefit for the population represented but... minimal risk/burden
Pregnant or breastfeeding women	•Direct benefit •No direct benefit but...relevant to this population...minimal risk/burden
Incapacitated subjects	•Direct benefit •Some benefit for the population represented by the incapacitated subject but...debilitating/life-threatening and minimal risk/burden
Additional national measures	•Persons in military service, persons deprived of liberty, or persons in residential care institutions.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

CTR - Transparency - increased availability of CT information and results

CTIS - publicly available information for authorised or refused trials:

- Application form
- Protocol
- Investigator's brochure
- Names of investigators and CVs
- Clinical trial sites
- Summary of CT results
- Assessment reports - final
- Inspection reports – final

Note: Requests for deferral, if agreed will be made public

Timing of public access depends on type of document and category of clinical trial

Maximum delay in the public access:

- Category I (phase I) - 7 years
- Category II (phase II & III) - 5 years
- Category III (Phase IV and low-intervention) - 1 year

General rule – quality parts of the IMPD will not be publically available

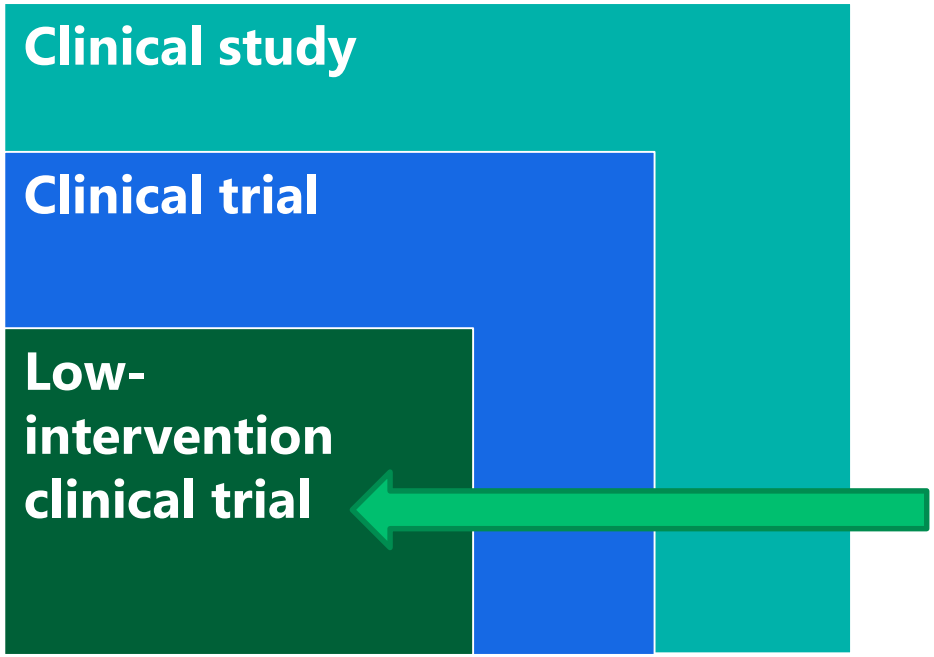
Transparency - exceptions

- CTIS shall be publicly accessible unless
  - personal data
  - commercially confidential information,
  - confidential communications between MSs re the assessment report,
  - effective supervision of the conduct of a clinical trial by MSs.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Other…

CTR - Definitions of level of intervention



Proposed by sponsor, and assessed by RMS.
Substantial modification – RMS will assess that CT remains low-intervention

CTR - Low-intervention CT

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

1	• the IMPs, excluding placebos, are authorised;
2	• IMPs used in accordance with the terms of the marketing authorisation; or • the use of the IMP is **evidence-based and supported by published scientific evidence** in any MSC
3	• the additional diagnostic or monitoring procedures do **not pose more than minimal additional risk or burden to the safety** of subjects compared to normal clinical practice in any MSC

Low intervention CT - Risk-based approach

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Monitoring by the sponsor

depending on …

- whether the clinical trial is a low-intervention clinical trial;
- the objective and methodology of the clinical trial
- the degree of deviation of the intervention from normal clinical practice

Traceability, storage, return , destruction of IMP

depending on …..

- whether the IMP is an authorised investigational medicinal product
- the clinical trial is a low-intervention clinical trial.

CTR - Statistics detail in the protocol

- timing of a planned interim analysis
- choice of sample size
- the number of subjects
- power calculations and and clinical relevance
- the level of significance to be used
- missing, unused, and spurious data and for reporting any deviation from the original statistical plan
- the selection of subjects to be included in the analyses

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Academic sponsors

- Co–sponsorship
- Report **SUSARs** to NCA for onward reporting to Eudravigilance, by arrangement

Supervision and controls

- MS supervision including inspections
- EC via ‘Union Controls’ will monitor whether MSs correctly supervise compliance with CTR

Implementation - what is HPRA doing?

- **EU**
  - **EMA** meetings/training events on CTR and CTIS
  - EC ad hoc group on clinical trials (**CTEG**) – NCAs and ethics committees
  - Clinical Trials Facilitation and Coordination Group (**CTFG**)
  - Coordination body (EMA/CTFG/EU commission)
  - **CTAG** – support best practices between MSs following implementation
- **National**
  - **National Office for Research Ethics Committees**
  - **Department of Health**
  - National contact point

Transition

Both CTD and **CTR** will apply for 3-year transition period beginning January 31, 2022

- CTD will apply to:
  - Clinical trials authorised under CTD to Jan 31, 2025
  - New clinical trials submitted within **one year** after implementation of the CTR, if the sponsor opts to apply under CTD i.e. Jan 31, 2023

  Note: All CTD trials must end or transition by January 31, 2025

CTR aims

- to create an **environment that is favourable** for conducting clinical trials
- with the **highest standards of patient safety**,
- **harmonise** decision-making
- foster **work sharing and collaboration** between Member States

Key message: CTR will be good for clinical research and clinical trial participants!

References

- Regulation 536/2014: https://ec.Europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
- Current and future Commission guidelines: https://ec.europa.eu/health/documents/eudralex/vol-10
- General Q+A: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
- Transition period:2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf (hma.eu)
- Transparency: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf
- Risk proportionate approaches: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf
- Auxiliary meds: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf
- Serious breaches: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf
- Commission training course March 2021: https://ec.europa.eu/health/human-use/events/ev_20210309_en

Thank you!

Health Products Regulatory Authority

CTReg@hpra.ie